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(54) Title: PLEASANT TASTING DRY POWDER COMPOSITIONS SUITABLE FOR PULMONARY DELIVERY

(57) Abstract: This invention discloses dry powder formulations suitable for pulmonary delivery, their methods of use and methods of manufacture wherein said formulations contain at least one drug substance with particle sizes less than about 10 microns and one or more taste masking substances with particle sizes greater than about 10 microns whereby the smaller drug substance particles largely flow into the respiratory tract while the larger taste masking particles, are more limited to the tongue and the back of the throat. This particular formulation is especially suitable for dry powder formulations comprising drug substances with bad taste.

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## **PLEASANT TASTING DRY POWDER COMPOSITIONS SUITABLE FOR PULMONARY DELIVERY**

### **FIELD OF THE INVENTION**

[0001] The present invention relates to dry powder inhalation drug compositions. In particular, those comprising an active drug substance having average particle diameter size sufficiently small enough to facilitate delivery of the drug substance to the respiratory tract, particularly the lower respiratory tract, and a pharmaceutical excipient or excipients containing at least one taste masking ingredient wherein the taste masking ingredient has an average particle diameter size sufficiently large enough to retain the taste masking ingredient substantially in the mouth or throat after administration.

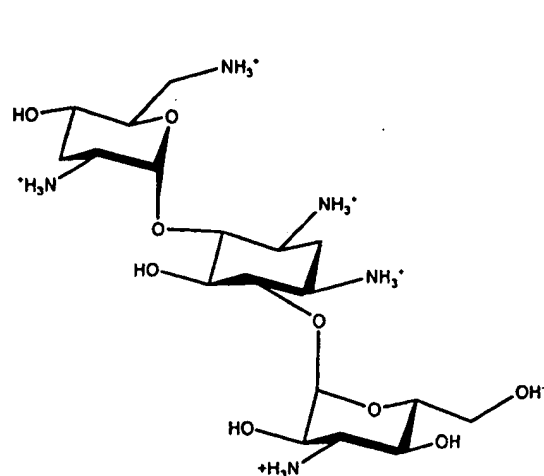
### **BACKGROUND OF THE INVENTION**

[0002] Oral delivery of drugs is the most common route of delivery since it provides minimal invasiveness to a person in need and typically enjoys the highest rate of compliance, but is not ideal for all drug substances. For example, in some cases oral delivery does not provide adequate bioavailability or an acceptable pharmacokinetic profile due to a particular drug substance's poor stability or absorption in the gastrointestinal tract. Accordingly, it is not always possible to get sufficient systemic exposure via the oral route. Alternatively, the oral dose necessary to achieve therapeutic effectiveness at a target tissue can require a systemic exposure well-above a side-effect free threshold and consequently decreases the utility of the particular agent being contemplated. In other cases, the time it takes for a drug to be absorbed via oral delivery can not satisfy the immediacy of the clinical need and thus a quicker route of administration can be desired.

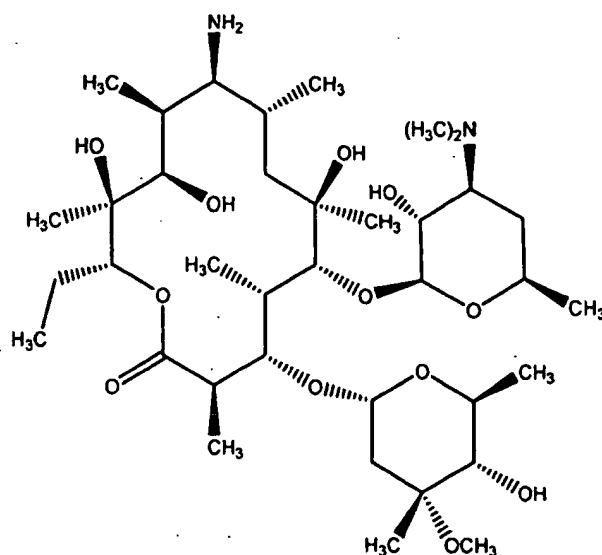
[0003] One class of drugs with poor oral bioavailability characteristics are the aminoglycoside antibiotics. The aminoglycosides are polar molecules that are protonated in the gut thus forming highly charged cationic species that are poorly absorbed (less than 1%) after oral administration. Furthermore, long term oral administration of these drugs can result in significant accumulation of the aminoglycoside in patients with impaired kidney function. While some of these problems can be obviated by parenteral administration of the aminoglycoside, there can still be problems of adequate tissue exposure where the desired bacterial target resides predominately in a tissue or area that has poor exposure to the

parenterally administered aminoglycoside. For example, bronchial infections require agents that can substantially penetrate the bronchial secretions without requiring continued and high systemic exposures to achieve such an effect. This is especially true for aminoglycosides because high systemic exposures can result in the risk of serious side effect including nephrotoxicity and ototoxicity. The penetration of parenterally administered aminoglycosides into bronchial secretions is poor and therefore this class of drugs must be given at high parenteral doses to achieve the desired effects when treating inhalation pathway infections and accordingly the side effects of the drugs becomes of increasing concern.

[0004] Tobramycin is an aminoglycoside produced from the actinomycete, *Streptomyces tenebrarius* and is a commonly prescribed aminoglycoside for the treatment of various bacterial infections including those infections caused by *P. aeruginosa*. Tobramycin, like other aminoglycosides is poorly absorbed across mucosal membranes and consequently has been given parenterally. Tobramycin's activity is diminished by purulent sputum because of the high concentration of divalent cations, acidic conditions, increased ionic strength and macromolecules that bind the drug with high affinity. It is therefore important that Tobramycin reach very high concentrations (5 to 10 times) of normally effective levels to be efficacious in such an environment. In order to solve the problem, it has been found that tobramycin can be administered via an aerosol formulation which allows for the treatment of patients with cystic fibrosis suffering from chronic *P. aeruginosa* infections as well as for the treatment of severe bronchitis or bronchiectasis caused by *P. aeruginosa*. Other classes of antibiotics such as the erythromycins (including for example, 9-(S)-erythromycylamine), have been investigated for administration by the inhalation route as well.



Tobramycin



9-(S)-erythromyclamine

[0005] One noted drawback in the pulmonary delivery of many drugs, and aminoglycoside antibiotics in particular is the poor or bitter taste associated with the compounds. Although the patient can become accustomed to the taste over time, concerns over patient comfort and compliance cannot be ignored. Accordingly, there is a large unmet need for drug formulations suitable for pulmonary delivery, particularly for those drugs with bad taste, to possess a taste that is more agreeable to the patient.

## Summary of the Invention

[0006] In some embodiments, this invention provides a dry powder composition suitable for inhalation comprising at least one drug substance having an average particle diameter size of between about 1 and about 10 microns and one or more taste masking agents wherein said taste masking agents have an average particle diameter size of greater than about 10 microns.

[0007] In some embodiments the at least one drug substance has an average particle diameter size of between about 1 and about 5 microns.

[0008] In some embodiments, the one or more taste masking agents has an average particle diameter size of between about 20 and about 150 microns.

[0009] In some embodiments, the one or more taste masking agents is selected from a group consisting of sweeteners, fragrances and flavorants, or combinations thereof.

[0010] In some embodiments the sweetener is selected from a group consisting of acesulfame potassium, aspartame, saccharin, saccharin sodium, sodium cyclamate, dextrose, lactose, mannitol, sorbitol, sucrose, xylitol, tagatose, lactitol, isomalt, thaumatin, neohesperidine and sucralose, or combinations thereof.

[0011] In some embodiments, the flavorant is selected from a group consisting of acetaldehyde, acetoin, aconitic acid, anethole, benzaldehyde, N-butyric acid, d- or l-carvone, cinnamaldehyde, citral, decanal, diacetyl, ethyl acetate, ethyl butyrate, ethyl vanillin, eugenol, geraniol, geranyl acetate, glycerol tributyrate, limonene, linalool, l-malic acid, methyl anthranilate, 3-methyl-3-phenyl glycidic acid ethyl ester, piperonal and vanillin, or combinations thereof.

[0012] In some embodiments, the dry powder formulations of this invention further comprise a surfactant or combination of surfactants. In some embodiments, the surfactant or combination of surfactants includes a phosphatidylcholine. In some embodiments, this invention includes a 1,2-diacylphosphatidylcholine. In some embodiments, the 1,2-diacylphosphatidyl choline is 1,2-distearoyl-sn-glycerol-3-phosphatidylcholine.

[0013] In some embodiments, the dry powder formulations of this invention further comprise a particle rigidifying excipient or combination of excipients. In some embodiments, the particle rigidifying excipient is  $\text{CaCl}_2$ .

[0014] In some embodiments, this invention includes a dry powder composition suitable for inhalation wherein the drug substance comprises an antibiotic and pharmaceutically acceptable salts thereof. In some embodiments, the antibiotic is an aminoglycoside and pharmaceutically acceptable salts thereof. In some embodiments, the aminoglycoside antibiotic is tobramycin, gentamycin, amikacin, netilmycin, kanamycin, streptomycin or neomycin, or a combination thereof and pharmaceutically acceptable salts thereof. In some embodiments, the aminoglycoside is tobramycin and pharmaceutically acceptable salts thereof.

[0015] In some embodiments, this invention describes a dry powder formulation comprising the following:

drug substance(s): 1% – 95%;

taste masking agent(s): 0.01% - 95%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 10 microns and the one or more taste masking agents have an average particle diameter size greater than about 10 microns. In some embodiments the at least one

drug substance has an average particle diameter size between about 1 and about 5 microns. In yet other embodiments, the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns.

**[0016]** In some embodiments, this invention provides a dry powder formulation comprising the following:

drug substance(s): 1% – 95%;

taste masking agent(s): 0.01% - 95%;

surfactant(s): 0.5% – 95%.

wherein the drug substances has an average particle diameter size of between about 1 and about 5 microns and the one or more taste masking agents has an average particle diameter size of between about 20 and about 150 microns and the one or more taste masking agents is selected from a group consisting of sweeteners, fragrances and flavorants, or combinations thereof.

**[0017]** In some embodiments, this invention provides a dry powder formulation comprising

drug substance(s): 1% – 95%;

taste masking agent(s): 0.01% - 95%;

surfactant(s): 0.5% – 95%;

particle rigidifying excipient(s): 0.1% - 20%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents has an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

**[0018]** In some embodiments, this invention provides a dry powder formulation comprising the following:

drug substance(s): 30% – 85%;

taste masking agent(s): 0.01% - 55%;

surfactant(s): 0.5% – 10%;

particle rigidifying excipient(s): 0.1% - 5%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking

agents are selected from a group consisting of sweeteners, fragrances, flavorants, or combinations thereof.

[0019] In some embodiments, this invention provides a dry powder formulation comprising the following:

drug substance(s): 50% – 70%;

taste masking agent(s): 0.01% - 20%;

surfactant(s): 1 – 5%;

particle rigidifying excipient(s): 0.5% - 3%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0020] In some embodiments, this invention provides a dry powder formulation comprising the following:

drug substance(s): 1% – 95%;

taste masking agent(s): 0.01% - 5%;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 0.5% – 95%;

particle rigidifying excipient(s): 0.1% - 20%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0021] In some embodiments, this invention provides a dry powder formulation comprising the following:

drug substance(s): 1% – 95%;

taste masking agent(s): 0.01% - 5%;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 0.5 – 95%;

CaCl<sub>2</sub>: 0.1% - 20%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking

agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

In some embodiments, this invention provides a dry powder formulation comprising the following:

tobramycin: 1% – 95%;  
taste masking agent(s): 0.01% - 5%;  
1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 0.5% – 95%;  
CaCl<sub>2</sub>: 0.1% - 20%.

wherein the drug substances has an average particle diameter size of between about 1 and about 5 microns and the one or more taste masking agents has an average particle diameter size of between about 20 and about 150 microns and the one or more taste masking agents is selected from a group consisting of sweeteners, fragrances and flavorants, or combinations thereof.

[0022] In some embodiments, this invention provides a dry powder formulation comprising the following:

tobramycin: 50% – 80%;  
sulfate: 15% – 25%;  
taste masking agent(s): 0.01% - 5%;  
1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 1-5%;  
CaCl<sub>2</sub>: 0.1% - 20%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0023] In some embodiments, this invention provides a dry powder formulation comprising the following:

tobramycin: 50% – 80%;  
sulfate: 15% – 25%;  
taste masking agent(s): 0.01% - 5%;  
1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 1-5%;  
CaCl<sub>2</sub>: 0.1% - 20%.



wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0024] In some embodiments, this invention provides a dry powder formulation comprising the following:

tobramycin: 58% – 62%;

sulfate: 19% – 25%;

taste masking agent(s): 0.01% - 5%;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 1% - 5%;

CaCl<sub>2</sub>: 0.5% - 1%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0025] In some embodiments, this invention provides a dry powder formulation comprising the following:

macrolide antibiotic(s): 1% – 95%;

taste masking agent(s): 0.01% - 95%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0026] In some embodiments, this invention provides a dry powder formulation comprising the following:

9-(S)-Erythromycylamine: 1% – 95%;

taste masking agent(s): 0.01% - 95%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking

agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0027] In some embodiments, this invention provides a dry powder formulation comprising the following:

9-(S)-Erythromycylamine: 1% – 95%;

taste masking agent(s): 0.01% - 95%;

surfactant(s): 0.5% – 95%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0028] In some embodiments, this invention provides a dry powder formulation comprising the following:

9-(S)-Erythromycylamine: 1% – 95%;

taste masking agent(s): 0.01% - 95%;

surfactant(s): 0.5% – 95%;

particle rigidifying excipient(s): 0.1% - 20%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0029] In some embodiments, this invention provides a dry powder formulation comprising the following:

9-(S)-Erythromycylamine: 60% – 95%;

HCl: 5% – 10%;

taste masking agent(s): 0.01% - 25%;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 5% – 25%;

CaCl<sub>2</sub>: 0.1% - 1.0%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking

agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0030] In some embodiments, this invention provides a dry powder formulation comprising the following:

9-(S)-Erythromyclamine: 75% – 85%;

HCl: 5% – 10%;

taste masking agent(s): 0.01% - 10%;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine: 5% – 10%;

CaCl<sub>2</sub>: 0.1% - 1.0%.

wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents is selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

[0031] In some embodiments, this invention describes a method of treating pulmonary bacterial infections comprising the administration by inhalation of a dry powder formulation suitable for inhalation wherein said dry powder formulation is comprised of:

a) an antibiotic possessing a mean particle diameter size between 1 and 5 microns;  
and

b) a taste masking agent or combination of taste masking agents wherein each taste masking agent has a mean particle diameter size greater than about 10 microns.

[0032] In some embodiments, this invention describes a method of treating pulmonary bacterial infections comprising the administration by inhalation of a dry powder formulation suitable for inhalation wherein said dry powder formulation is comprised of:

a) tobramycin or 9-(S)-Erythromyclamine and pharmaceutically acceptable salts possessing a mean particle diameter size between about 1 and about 5 microns; and

b) a taste masking agent or combination of taste masking agents wherein each taste masking agent has a mean particle diameter size greater than about 10 microns.

[0033] In some embodiments, said pulmonary bacterial infection to be treated is caused by *aeruginosa*, *klebsiella*, *enterobacter*, *e.coli*, *serratia* or *siaureus*, or combinations thereof.

[0034] In some embodiments, the method of treatment of a pulmonary bacterial infection includes a taste masking agent or combination of agents having a mean diameter size between about 20 and about 150 microns.

[0035] In some embodiments, the method of treating a pulmonary bacterial infection further comprises a surfactant. In some embodiments, the surfactant is a phosphatidylcholine. In some embodiments, said phosphatidylcholine is 1,2-distearoyl-sn-glycerol-3-phosphatidylcholine.

[0036] In some embodiments, the method of treating a pulmonary bacterial infection further comprises a particle rigidifying excipient. In some embodiments, the particle rigidifying excipient is  $\text{CaCl}_2$ .

[0037] In some embodiments, this invention provides a method of manufacturing a dry powder formulation suitable for inhalation comprising the combining of one or more drug substances with an average particle diameter size of about 1 to about 5 microns with one or more taste masking agents having an average particle diameter size greater than about 10 microns.

[0038] In some embodiments, the drug substance average diameter particle size of about 1 to about 5 microns is produced by spray drying. In some embodiments, the spray drying is performed with one or more surfactants. In some embodiments, the surfactant is a diphosphatidylcholine. In some embodiments, the diphosphatidylcholine is 1,2-distearoyl-sn-glycerol-3-phosphatidylcholine.

[0039] In some embodiments, the spray drying is performed with one or more particle rigidifying excipients. In some embodiments, one of the particle rigidifying excipients is  $\text{CaCl}_2$ .

[0040] In some embodiments, one or more blowing agents is used in the spray drying process. In some embodiments, the one or more blowing agents includes at least one fluorocarbon or fluorohalocarbon. In some embodiments, the fluorohalocarbon is perfluorooctyl bromide.

[0041] In some embodiments, the taste masking agent used in any of the embodiments of the methods of manufacture has a mean average diameter particle size of between about 20 and about 150 microns.

[0042] In some embodiments, the combining of one or more drug substances and the one or more taste masking agents is performed by dry blending.

## Detailed Description of the Invention

[0043] The present invention provides compositions suitable for pulmonary administration with the advantage of masking the poor taste of many drugs that are delivered by a pulmonary route.

[0044] The terms "pulmonary" or "pulmonary delivery" refer to all manners of delivery wherein a drug substance is brought into direct contact with all or any portion of the respiratory tract, including the lower respiratory tract. The drug substance can be formulated so as to be suitable for aerosolization or for dry powder inhalation, preferably for dry powder inhalation. The formulated drug particle size can vary according to the size deemed to be optimal for pulmonary delivery. Generally, drug particle size must be formulated to be suitably small so that when the formulation is aspirated, the drug particle is taken into the lower respiratory tract. Accordingly, drug particle sizes are typically less than about 100 microns in diameter, or preferably less than about 50 microns, or more preferably less than about 25 microns, or less than about 10 microns or from between about 1 and about 5 microns. The dosages of the drug will vary depending on, *inter alia*, the size of the patient, the condition being treated, and the drug being used. For dry powder formulations, the selected drug can be any drug that can be effectively and safely delivered via the pulmonary route.

[0045] Drug substances contemplated for use in this invention, alone or in combination with one or more other drug substances, include by way of the following non-limiting examples, muscarinic receptor agonists and antagonists (such as acetylcholine, muscarine, pilocarpine, tolterodine atropine and the like), anticholinesterase agents (such as physostigmine, donepezil, huperzine A, selegine, tacrine, rivastigmine and the like), nicotine,  $\beta$ -adrenergic agonists (such as isoproterenol, dobutamine, metaproterenol, terbutaline, albuterol, salmeterol, ritodrine and the like),  $\alpha_1$ -selective adrenergic agonists (such as methoxamine, phenylephrine, mephentermine, mataraminol, milodrine, clonidine, guanabenz, methyldopa and the like), decongestants (such as ephedrine, pseudoephedrine and the like), stimulants (such as methylphenidate, amphetamine and the like), adrenergic receptor antagonists (such as indoramin, yohimbine, doxazosin, prazosin and the like),  $\beta$ -adrenergic receptor antagonists (such as propranolol, metoprolol, atenolol, nadolol, timolol, pindolol and the like), serotonin receptor agonists and antagonists (such as sumatriptan, zolmitriptan, olanzapine, risperdal, haldol, fluoxetine, fluvoxamine, sertraline, reboxetine, venlafaxine and

the like), systemic anesthetics, sedatives, hypnotics, tranquilizers, sleep inducing agents (such as ambien, zaleplon and the like), anticonvulsants and antiepileptics (such as phenytoin, primidone, valproate, zonisamide, tiagabine, carbamazepine, ethosuximide, gabapentin, topiramate, and the like), analgesics (such as dynorphin, endorphin, enkephalin, morphine, codeine, fentanyl, methadone and the like), histidine receptor antagonists (such as diphenylhydramine, loratidine and the like), anti-inflammatory drugs (such as indomethacin, ketoprofen, ibuprofen, etodolac, sulindac, celecoxib, naproxen, rofecoxib and the like), leukotriene-receptor antagonists (such as zafirlukast, montelukast, zileuton and the like), diuretics, vasopressin agonists and antagonists, renin antagonists, angiotensin converting enzyme inhibitors (such as captopril, enalapril, lisinopril and the like), angiotensin II antagonists (such as losartan, valsartan, candesartan and the like), antiarrhythmics, statins, fibrates, proton pump inhibitors, H<sub>2</sub>-antagonists, antifungal agents (such as fluconazole, itraconazole, ketoconazole and the like), antiviral agents (such as acyclovir, ganciclovir, cidofovir, amantadine, zanamivir, zanamivir, ribavirin, efavirenz, nevirapine, delaviridine, indinavir, saquinavir, ritonavir, lopinavir, and the like), antineoplastics, antimitotics, antitumor antibiotics, immunosuppressants, thrombolytics, thyroidics, antithyroidics, estrogens, progestins, androgens, glucocorticoids (such as cortisol, cortisone, prednisone, dexamethasone and the like), antiglucocorticoids, insulin, insulin mimetics, sulfonylureas, thiazolinediones, vitamins, nucleotides, nucleosides, antisense polynucleosides and peptide and protein-based therapeutics.

[0046] Many types of antibiotics can be administered in the manner according to this invention, such as, but not limited to, aminoglycosides, beta-lactams, macrolides, quinolones and fluoroquinolones, sulphonamides and tetracyclines. Aminoglycoside antibiotics include such drugs as tobramycin, gentamycin, amikacin, netilmycin, kanamycin, streptomycin or neomycin. Macrolide antibiotics include such drugs as azithromycin, clarithromycin, erythromycin, leucomycin, macrocin, cirramycin, concanamycin, midecamycin, or chalcocomycin. Erythromycins include such compounds as 9-(S)-erythromycylamine.

[0047] In order to formulate the drug substance for dry powder formulation, the desired compound or its pharmaceutically acceptable salt must be made into a substance with the desired median diameter particle size. This can be accomplished by one or more of various methods, alone or in combination, including, but not limited to, milling, spray-drying or precipitation to a powder having the desired mass median diameter which is typically, less than about 100 microns, or less than about 50 microns, or less than about 25 microns or less

than about 10 microns or from between about 1 and about 5 microns. The milling can be accomplished by any method known to those of skill in the art such as jet milling or media milling. Jet milling techniques involves the use of air blown at high velocity causing the particles to collide with one another until they achieve the desired median diameter. Media milling can be performed by tumbling the drug substance in a mill containing ceramic, glass or steel objects such as balls until the drug substance obtains the desired median diameter. The size of the particles can be determined by various methods known to those of skill in the art including light scattering techniques. Spray drying techniques involve the spraying of a solution containing the drug substance in fine particles onto a surface where the particles are then dried and the particles of the desired size recovered.

[0048] Precipitation is performed by putting the drug substance in a solvent and adding another solvent. The drug substance needs to have a decreased solubility in the mixed solvent system, thus forcing its precipitation from solution. The drug substance of desired size then can be collected by filtration, centrifugation or solvent evaporation. Precipitation also can be accomplished by placing the drug substance in a solvent where the drug substance has little solubility at a given temperature but increased solubility at a higher temperature. The solution then can be heated until the desired amount of dissolution takes place and subsequently cooled at a rate and in a manner appropriate for achieving the desired median particle size.

[0049] The drug substance will be one or more components of the final composition. Accordingly, the at least one drug substance can be present in from about 0.1% to about 99% by weight of the total composition; or from about 0.1% to about 95%, or from about 0.1% to about 80%, or from about 0.1% to about 50%, or from about 0.1% to about 25%, or from about 0.1% to about 10%, or from about 0.1% to about 5%, or from about 0.1% to about 1%, or from about 1% to about 99%, about 1% to about 95%, or from about 1% to about 80%, or from about 1% to about 50%, or from about 1% to about 25%, or from about 1% to about 10%, or from about 1% to about 5%, or from about 5% to about 99%, or from about 5% to about 95%, or from about 5% to about 80%, or from about 5% to about 50%, or from about 5% to about 25%, or from about 5% to about 10%, or from about 10% to about 99%, or from about 10% to about 95%, or from about 10% to about 80%, or from about 10% to about 50%, or from about 10% to about 25%, or from about 20% to about 99%, or from about 20% to about 95%, or from about 20% to about 80%, or from about 20% to about 50%, or from about 20% to about 25%, or from about 30% to about 99%, or from about 30% to about 95%,

or from about 30% to about 80%, or from about 30% to about 50%, or from about 30% to about 40%, or from about 40% to about 99%, or from about 40% to about 95%, or from about 40% to about 80%, or from about 40% to about 50%, or from about 50% to about 70%, or from about 55% to about 65%, or from about 58% to about 62%, or from about 75% to about 85%, or from about 80% to about 85%.

[0050] The drug substances used in the formulations of this invention can exist as pharmaceutically acceptable salts, including pharmaceutically acceptable acid addition salts prepared from pharmaceutically acceptable acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Further representative examples of pharmaceutically acceptable salts can be found in, *Journal of Pharmaceutical Science*, 66, 2 (1977), incorporated herein by reference. Reacting compounds of this invention with one or more equivalents of an appropriately reactive base can also prepare basic salts. Both mono and polyanionic salts are contemplated, depending on the number of acidic hydrogens available for deprotonation. Appropriate bases can be either organic or inorganic in nature. For example, inorganic bases such as  $\text{NaHCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{KHCO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{Cs}_2\text{CO}_3$ ,  $\text{LiOH}$ ,  $\text{NaOH}$ ,  $\text{KOH}$ ,  $\text{NaH}_2\text{PO}_4$ ,  $\text{Na}_2\text{HPO}_4$ ,  $\text{Na}_3\text{PO}_4$  as well as others are suitable. Organic bases including amines, alkyl amines, dialkylamines, trialkylamines, various cyclic amines (such as pyrrolidine, piperidine, etc.) as well as other organic amines are suitable. Quaternary ammonium alkyl salts can also be prepared by reacting an amine-containing compound of the invention with an appropriately reactive organic electrophile (such as methyl iodide or ethyl triflate). Furthermore, where a drug substance has multiple acidic or basic sites, or combinations thereof, it is possible that more than one equivalent of acids, bases or combinations thereof can be used to prepare the drug substance containing multiple counterions and all such combinations are part of the scope of this invention.

[0051] References to ranges of drug substances as percentages by weight of drug per weight of composition refer to the active moiety free of any counter ions. Bulk density ranges refer to the density of the specific composition or component being referred to.



[0052] Bulk densities of the drug substance will typically be less than  $0.25 \text{ g/cm}^3$ . In some embodiments, the bulk density of the drug substance will be less than  $0.1 \text{ g/cm}^3$ . In yet other embodiments, the bulk density of the drug substance will be less than  $0.05 \text{ g/cm}^3$ .

[0053] In order to formulate the ultimate product suitable for pulmonary administration, including dry powder formulations for inhalation, this invention requires the further inclusion of at least one taste-masking agent in a particle size greater than the particle size of the drug substance. Thus, when the drug substance is aspirated into the respiratory tract, the taste masking particles, having a greater diameter will not penetrate to the lower respiratory tract to the same relative extent that the drug substance does. Accordingly, the taste masking particles will be deposited in a more concentrated fashion where taste is perceived such as on the tongue, in the mouth and at the back of the throat, to a greater extent than the drug substance. Formulations thus composed will therefore have a good taste and will help mask the bad taste associated with some products designed for pulmonary delivery, such as dry powder formulations for inhalation. The desired median diameter size for the taste masking agent(s) will be larger than the formulated drug substance median diameter particle size.

[0054] The median diameter size of the taste masking particles can be greater than about 10 microns, greater than about 20 microns, greater than about 50 microns, greater than about 150 microns or between about 10 and about 500 microns, or between about 10 and about 250 microns, or between about 10 and about 150 microns, or between about 10 and about 100 microns, or between about 20 and about 500 microns, or between about 20 and about 250 microns, or between 20 and about 200 microns, or between about 20 and about 150 microns, or between about 20 and about 100 microns, or between about 30 and about 1000 microns, or between about 30 and about 500 microns, or between about 30 and about 250 microns, or between about 30 and about 200 microns, or between about 30 and about 100 microns, or between about 50 and about 1000 microns, or between about 50 and about 500 microns, or between about 50 and about 250 microns or between about 20 and about 150 microns. Where multiple taste masking agents are employed, the median particle size for each agent can be independently selected from one of the identified ranges. The particles of this invention including the drug substance(s) and taste masking agent(s) can be of any general shape including spherical.

[0055] The taste masking agent(s) are present in the final composition in an amount suitable to at least partially mask the flavor of the active drug(s) in preferred embodiments.

The flavor of the active drug is completely masked. The exact quantity depends upon the identity of the taste masking agent(s) and the active drug(s) whose flavor needs to be masked. The amount of taste masking agent(s) can be present in an amount of from about 0.01% to about 95% of the total weight of the formulation. In some embodiments, the taste masking agent or combination of taste masking agents can be present in an amount of from about 0.01% to about 75%, or from about 0.01% to about 55%, or from about 0.01% to about 25%, or from about 0.01% to about 5%, or from about 0.01% to about 3%, or from about 0.01% to about 1%, or from about 0.01% to about 0.5%, or from about 0.01% to about 0.3%, or from about 0.01% to about 0.1%, or from about 0.01% to about 0.05%, or from about 0.02% to about 5%, or from about 0.02% to about 3%, or from about 0.02% to about 1%, or from about 0.02% to about 0.5%, or from about 0.02% to about 0.1%, or from about 0.02% to about 0.05%, or from about 0.04% to about 5%, or 0.04% to about 3%, or from about 0.04% to about 1%, or from about 0.04% to about 0.5%, or from about 0.04% to about 0.1%, or from about 0.1 to about 5%, or from about 0.1% to about 3%, or from about 0.1% to about 1%, or from about 0.1% to about 0.5%.

[0056] The taste masking agents can be selected from agents known to those of skill in the art to be sweetening, flavoring, fragrances or any other materials known to those of skill in the art to be useful as taste masking agents. To achieve the desired affect a combination of these agents can be used. Taste masking agents can work primarily by action on the taste buds but can also work by fragrance alone. The taste masking agent can provide a combination of a scent and taste agent. The taste masking agent can consist of a combination of sweeteners, fragrances and/or flavoring agents. The taste masking agents can be selected from any artificial and/or natural flavoring agents known to those of skill in the art, such as those listed in the FDA GRAS list of flavorings, which is herein incorporated by reference. Such flavoring agents can be selected alone or in combination from acetaldehyde, acetoin, aconitic acid, anethole, benzaldehyde, N-butyric acid, d- or l-carvone cinnamaldehyde, citral, decanal, diacetyl, ethyl acetate, ethyl butyrate, ethyl vanillin, eugenol, geraniol, geranyl acetate, glycerol tributyrate, limonene, linalool, l-malic acid, methyl anthranilate, 3-methyl -3-phenyl glycidic acid ethyl ester, piperonal, vanillin, and others.

[0057] Sweeteners include but are not limited to such substances as acesulfame potassium, aspartame, saccharin, saccharin sodium, sodium cyclamate, dextrose, lactose, mannitol, sorbitol, sucrose, xylitol, tagatose, lactitol, isomalt, thaumatin, neohesperidine, and sucralose. Taste masking agents incorporating lactose are always defined to include at least

one or more additional sweeteners, fragrances and flavorants, and the provided ranges of weight percentages for said sweeteners, fragrances and flavorants is exclusive of any included lactose.

[0058] The composition suitable for pulmonary administration can contain additional components or materials to aid in formulation stability, dispersability, and the like. For example, the composition can include a surfactant or other material to help prevent drug particle aggregation. Surfactants are included to aid in the formation of perforated microparticles or provide enhanced suspension stability, improved powder dispersability or decreased particle aggregation. The surfactant can be a single compound or a combination of more than one compounds. Surfactants can be present in the form of lipids, detergents or polymers, ionic or non-ionic. Lipids include fatty acids and phospholipids. Particularly suitable phospholipids include phosphatidylinositols, phosphatidylserines, phosphatidylcholines including 1,2-diacyl phosphatidylcholines such as 1,2-distearoyl-sn-glycerol-3-phosphatidylcholine and the like. Fatty acids include such moieties as oleic acid, stearic acid and the like. Where surfactants are utilized, they can be utilized singly or in combination. The surfactants used can be employed in ranges expressed as weight percentage ranges of the total formulation weight of from about 0.1% to about 99%, 0.1% to about 95%, or from about 0.1% to about 75%, or from about 0.1% to about 50%, or from about 0.1% to about 25% or from about 0.1% to about 10%, or from about 0.5% to about 95%, or from about 0.5% to about 75%, or from about 0.5% to about 50%, or from about 0.5% to about 25% or from about 0.5% to about 10%; or from about 0.5% to about 5%, or from about 1% to about 99%, 1% to about 95%, or from about 1% to about 75%, or from about 1% to about 50%, or from about 1% to about 25% or from about 1% to about 10%, or from about 1 to about 5%, or from about 3% to about 99%, 3% to about 95%, or from about 3% to about 75%, or from about 3% to about 50%, or from about 3% to about 25% or from about 3% to about 10%, or from about 3 to about 5%, 3 to about 4%, or from about 5 to about 99%, 5% to about 95%, or from about 5% to about 75%, or from about 5% to about 50%, or from about 5% to about 25% or from about 5% to about 10%, or from about 7% to about 99%, 7% to about 95%, or from about 7% to about 75%, or from about 7% to about 50%, or from about 7% to about 25% or from about 7% to about 10%, or from about 8 to about 10%, or from about 9 to about 10%.

[0059] In addition to the surfactant, additional excipients can be utilized in order to improve particle rigidity (hereinafter referred to as particle rigidifying excipients) include

various carbohydrates such as dextrose, lactose, raffinose and the like, amino acids such as glycine and the like, inorganic salts such as sodium chloride, potassium chloride, calcium chloride and the like, organic salts such as sodium acetate, sodium ascorbate and the like. Particle rigidifying excipients can be used alone or in combination and are suitably employed in amounts from about 0.01% to about 20%, or from about 0.01% to about 10%, or from about 0.01% to about 5%, or from about 0.01% to about 3%, or from about 0.01% to about 1%, or from about 0.01% to about 0.9%, or from about 0.01% to about 0.8%, or from about 0.01% to about 0.7%, or from about 0.01% to about 0.6%, or from about 0.01% to about 0.5% or from about 0.01% to about 0.1%, or from about 0.01% to about 0.05%, or from about 0.05% to about 20%, or from about 0.05% to about 10%, or from about 0.05% to about 5%, or from about 0.05% to about 3%, or from about 0.05% to about 1%, or from about 0.05% to about 0.9%, or from about 0.05% to about 0.8%, or from about 0.05% to about 0.7%, or from about 0.05% to about 0.6%, or from about 0.05% to about 0.5% or from about 0.05% to about 0.1%, from about 0.1% to 20%, or from about 0.1% to 10%, or from about 0.1% to 5%, or from about 0.1% to about 3%, or from about 0.1% to about 1%, or from about 0.1% to about 0.9%, or from about 0.1% to about 0.8%, or from about 0.1% to about 0.7%, or from about 0.1% to about 0.6%, or from about 0.1% to about 0.5%, or from about 0.2% to about 20%, or from about 0.2% to about 10%, or from about 0.2% to about 5%, or from about 0.2% to about 3%, or from about 0.2% to about 1%, or from about 0.2% to about 0.9%, or from about 0.2% to about 0.8%, or from about 0.2% to about 0.7%, or from about 0.2% to about 0.6%, or from about 0.2% to about 0.5%, 0.3% to about 20%, or from about 0.3% to about 10%, or from about 0.3% to about 5%, or from about 0.3% to about 3%, or from about 0.3% to about 1%, or from about 0.3% to about 0.9%, or from about 0.3% to about 0.8%, or from about 0.3% to about 0.7%, or from about 0.3% to about 0.6%, or from about 0.3% to about 0.5%, or from about 0.4% to about 20%, or from about 0.4% to about 10%, or from about 0.4% to about 5%, or from about 0.4% to about 3%, or from about 0.4% to about 1%, or from about 0.4% to about 0.9%, or from about 0.4% to about 0.8%, or from about 0.4% to about 0.7%, or from about 0.4% to about 0.6%, or from about 0.4% to about 0.5%, 0.5% to about 20%, or from about 0.5% to about 10%, or from about 0.5% to about 5%, or from about 0.5% to about 3%, or from about 0.5% to about 1%, or from about 0.5% to about 0.9%, or from about 0.5% to about 0.8%, or from about 0.5% to about 0.7%, or from about 0.5% to about 0.6%, or from about 0.6% to about 20%, or from about 0.6% to about 10%, or from about 0.6% to about 5%, or from about 0.6% to about 3%, or from about 0.6% to about 1%,

or from about 0.6% to about 0.9%, or from about 0.6% to about 0.8%, or from about 0.6% to about 0.7%, or from about 0.8% to about 0.9%.

**[0060]** The final formulation can also include acceptable pharmaceutical excipients which can serve as drying agents, carriers and the like. For example, a carrier can be used that is comprised of a bulking agent that includes essentially inert excipients known to those of skill in the art.

**[0061]** In cases where the micronized particles including a surfactant are prepared via spray drying, a blowing or inflating agent can be used during the particle manufacture for increasing dispersability of the perforated microstructures. The blowing agent used is typically a liquid agent which can be evaporated off during the process include polyfluorohydrocarbons (such as perfluorohexane and the like), polyfluorohalohydrocarbons (such as perfluorooctyl bromide and the like), freons, esters, alcohols and hydrocarbons and the like.

**[0062]** The taste masking agent and any additional excipients that are likewise not desired to have the same median particle diameter as the drug substance can be separately milled, precipitated or spray dried to render the desired median diameter particle size. The final formulation then can be prepared by combining to essential homogeneity the various components of the desired formulation. The components for the final formulation can be combined by any method which preserves the particle size and integrity of the respective components. By way of non-limiting example, the individual ingredients or formulation components can be combined by dry blending.

**[0063]** The dry powders of this invention will typically have moisture contents of less than 10% by weight. In some embodiments, the moisture content is less than 6% by weight. In some embodiments, the moisture content is less than 3% by weight. In some embodiments, the moisture content is less than 1% by weight.

**[0064]** The methods of administering the formulations of this invention include any methods wherein the agent is insufflated, aspirated or inhaled through the nasal or oral cavity. These methods include, but not limited to, delivery via aerosol, colloid or dry powder formulation. The drug composition can be administered by dry powder inhaler, metered dose inhaler or nebulizer.

**[0065]** Another aspect of this invention provides a method of treating illness by inhalation of dry powder formulations containing one or more drug substances of mean particle size diameter of less than about 10 microns or from about 1 to about 5 microns, or

any of the ranges previously described for drug particle size of compositions of this invention together with one or more taste masking agents having an average mean particle size diameter greater than the average mean particle diameter size of the drug substances, or typically greater than about 10 microns, or from about 20 to about 150 microns, or in any suitable range as described previously in the description of the taste masking agent composition components of this invention. The particular treatment mode including the amount administered will depend on several variables including the particularities of the individual being treated, the disease or illness being treated, the drug or drug combination being used, other medicines or drugs being used, etc. Accordingly, such determinations are typically made by the medical practitioner or any other individual of suitable skill in the art including the individual being treated, by taking into account the many variables as well as the individual practitioner's own experience and assessment. In some embodiments, this invention provides a method of treating bacterial infections by the pulmonary delivery of a drug substance or substances, preferably an antibiotic of suitable mean diameter particle size, coupled with one or more taste masking substances wherein said taste masking substances are of greater mean diameter particle size than that of the drug substance(s). For example, in some instances the drug substances used in the methods of treatment can have a mean particle size diameter of less than about 10 microns or from about 1 to about 5 microns, or any of the ranges previously described for drug particle size of compositions of this invention together with one or more taste masking agents having an average mean particle size diameter greater than the average mean particle diameter size of the drug substances, or greater than about 10 microns, or from 20 to 150 microns, or in any suitable range as described previously in the description of the taste masking agent composition components of this invention. In some aspects of this invention, the antibiotic used in the treatment methods of this invention is any aminoglycoside or macrolide suitable for pulmonary administration. For example, the aminoglycoside tobramycin and the macrolide 9-(S)-Erythromycylamine are useful antibiotics in the method of treatments of this invention. Many bacterial infections can be treated by pulmonary delivery of an appropriate antibiotic and the methods of treatment of this invention embrace all such uses. By way of non-limiting examples, the bacterial strains *aeruginosa*, *klebsiella*, *enterobacter*, *e.coli*, *serratia* and *siaureus*, or combinations thereof are all suitable targets of the methods of this invention. The methods of treatment of this invention also describe the administration of the compositions of this invention wherein the

compositions can also comprise surfactants and particle rigidifying excipients as described previously for the composition descriptions.

[0066] This invention also describes methods for the manufacture of the novel compositions described herein. For example, the compositions of this invention can be prepared by combining the individual components of the invention. In such a way, a drug substance(s) of the appropriate or preferred particle diameter size can be combined with the taste masking agent(s) of the appropriate or preferred particle diameter size. The method of manufacture also describes methods for preparation of the particles of appropriate size. For example, drug substance particles of the appropriate size can be prepared by spray drying and the spray drying process can be performed in the presence of one or more surfactants of suitable identity. An appropriate surfactant, is in some cases, for example, a diphosphatidylcholine and in some cases is 1,2-distearoyl-sn-glycerol-3-phosphatidylcholine. The methods of manufacture of this invention also can include in the spray drying process, one or more particle rigidifying excipients for example calcium chloride. Additionally, the methods of manufacture of this invention can also include one or more blowing agents in the spray drying process such as one or more fluorocarbon or fluorohalocarbon such as perfluorooctyl bromide. In some embodiments of this invention, the individual components of the final composition are combined via dry blending.

[0067] The following examples serve to illustrate some of the embodiments of the invention. The examples provide the preparation of certain exemplary formulations as well as lists several component examples. The examples serve only to highlight some of the potential formulations and should not be read to limit the invention in any way.

**Example I General Preparation of Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder Inhalation**

[0068] Tobramycin sulfate perforated microstructures are prepared via a spray drying technique using 80-100% aspiration with a suitable spray drier, such as a B-191 Mini Spray-Drier at an inlet temperature range of from about 80°C to 100°C with an outlet temperature of from about 50°C to 70°C; inert gas flow (N<sub>2</sub> or Ar) of from about 500 L/hr to 5,000 L/hr. Emulsion solutions of tobramycin sulfate are prepared via preparing a mixture of tobramycin sulfate 40-80%; surfactant 1 to 20%; group I or II metal halide (0 to 5 %); blowing agent (added to suit, see below).

[0069] A surfactant as well as the group I or II metal halide in predetermined amounts are added to deionized water and vigorously mixed. During the mixing process, optional surfactant is added slowly and after complete addition, the mixture is mixed further until achieving the desired emulsion consistency. At this point, the mixture can be further homogenized under high pressure using a suitable commercial homogenizer. Tobramycin sulfate in water is added to the surfactant/group I or II metal halide/blowing agent emulsion and the combined emulsion mixed further and spray dried according to the spray-drying parameters outlined above.

[0070] The free flowing powder thus formed is analyzed for mean particle diameter determination. If the mean particle diameter determination indicates that the particles are still too great in size for the particular dry powder formulation, further particle size reduction by milling or precipitation can be contemplated. Alternatively, the spray drying process described above can be repeated but the parameters varied in order to achieve the desired particle size.

[0071] With the tobramycin sulfate of suitable particle size and porosity in hand, the final formulation blending can be performed. This process requires the mixing or dry blending of the taste-masking agent(s) with the tobramycin sulfate. Additional excipients such as bulking agents or carrier agents, colorants, etc. can be included as well.

[0072] Examples II to XXI, below, can also be made following this general procedure.

**Example II Pleasant Tasting Tobramycin Sulfate Powder Suitable for Dry  
Powder Inhalation**

Tobramycin 20-80%

Sulfate 10-30%

Surfactant 1-10%

Particle rigidifying excipient 0.2 to 5%

Taste masking agent(s) 0.01 to 95%

Additional optional excipients up to 10%



**Example III Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 40-80%

Sulfate 15-30%

Surfactant 1-10%

Particle rigidifying excipient 0.2 to 2%

Taste-masking agent 0.01% to 50%

Additional optional excipients up to 10%

**Example IV Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 50-70%

Sulfate 18-25%

Surfactant 1-5%

Particle rigidifying excipient 0.5 to 1.5%

Taste-masking agent 0.01% to 25%

Additional optional excipients up to 10%

**Example V Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 55-65%

Sulfate 20-25%

Surfactant 2-4%

Particle rigidifying excipient 0.5 to 1.5%

Taste-masking agent 0.05% to 5%

Additional Optional Excipients up to 10%

**Example VI Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 55-65%

Sulfate 20-25%

1,2-Distearoyl-sn-glycero-3-phosphocholine 2-4%

CaCl<sub>2</sub> 0.5 to 1.5%

Taste-masking agent 0.05% to 2%

Additional optional excipients up to 10%

**Example VII Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 55-65%

Sulfate 20-25%

1,2-Distearoyl-sn-glycero-3-phosphocholine 2-4%

CaCl<sub>2</sub> 0.5 to 1.5%

Xylitol 0.05% to 2%

Additional optional excipients up to 10%

**Example VII Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 55-65%

Sulfate 20-25%

1,2-Distearoyl-sn-glycero-3-phosphocholine 2-4%

CaCl<sub>2</sub> 0.5 to 1.5%

Xylitol 0.05% to 2%

Additional optional excipients up to 10%

**Example VIII Good Tasting Tobramycin Sulfate Powder Suitable for Dry**

**Powder Inhalation**

Tobramycin 55-65%

Sulfate 20-25%

1,2-Distearoyl-sn-glycero-3-phosphocholine 2-4%

CaCl<sub>2</sub> 0.5 to 1.5%

Aspartame 0.05% to 2%

Additional optional excipients up to 10%

**Example IX Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 61.5%  
Sulfate 22.4%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 3.3%  
CaCl<sub>2</sub> 0.9%  
Aspartame 0.5%  
Lactose 11.3%

**Example X Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 61.5%  
Sulfate 22.4%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 3.3%  
CaCl<sub>2</sub> 0.9%  
Limonene 0.5%  
Lactose 11.3%

**Example XI Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 61.5%  
Sulfate 22.4%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 3.3%  
CaCl<sub>2</sub> 0.9%  
Sorbitol 0.5%  
Lactose 11.3%

**Example XII Good Tasting Tobramycin Sulfate Powder Suitable for Dry Powder**

**Inhalation**

Tobramycin 61.5%  
Sulfate 22.4%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 3.3%  
CaCl<sub>2</sub> 0.9%  
Geraniol 0.2%  
Sucralose 0.3%  
Lactose 11.3%

**Example XIII Good Tasting Tobramycin Sulfate Powder Suitable for**

**Aerosolization**

Tobramycin 61.5%  
Sulfate 22.4%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 3.3%  
CaCl<sub>2</sub> 0.9%  
Limonene 0.2%  
Sorbitol 0.3%  
Lactose 11.3%

**Example XIV Good Tasting Tobramycin Sulfate Powder Suitable for Dry**

**Powder Inhalation**

Tobramycin 61.5%  
Sulfate 22.4%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 3.3%  
CaCl<sub>2</sub> 0.9%  
Limonene 0.2%  
Aspartame 0.3%  
Lactose 11.3%

**Example XV Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for  
Dry Powder Inhalation**

9-(S)-erythromyclamine 70-95%  
HCl 4-12%  
Surfactant 1-20%  
Particle rigidifying excipient 0.2 to 5%  
Taste masking agent(s) 0.01 to 10%  
Additional optional excipients up to 10%

**Example XVI Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for  
Dry Powder Inhalation**

9-(S)-erythromyclamine 75-90%  
HCl 4-8%  
Surfactant 5-20%  
Particle rigidifying excipient 0.2 to 2%  
Taste masking agent(s) 0.01 to 5%  
Additional optional excipients up to 10%

**Example XVII Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for  
Dry Powder Inhalation**

9-(S)-erythromyclamine 80-95%  
HCl 4-8%  
Surfactant 8-15%  
Particle rigidifying excipient 0.2 to 2%  
Taste masking agent(s) 0.1 to 2%  
Additional optional excipients up to 10%

**Example XVIII Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for Dry Powder Inhalation**

9-(S)-erythromyclamine\_75-85%  
HCl 5-8%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 5-10%  
CaCl<sub>2</sub> 0.5 to 1.5%  
Taste-masking agent 0.05% to 2%  
Additional optional excipients up to 10%

**Example XIX Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for Dry Powder Inhalation**

9-(S)-erythromyclamine\_83.0%  
HCl 6.5%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 9.3%  
CaCl<sub>2</sub> 0.7%  
Limonene 0.2%  
Aspartame 0.3%

**Example XX Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for Dry Powder Inhalation**

9-(S)-erythromyclamine\_83.0%  
HCl 6.5%  
1,2-Distearoyl-sn-glycero-3-phosphocholine 9.3%  
CaCl<sub>2</sub> 0.7%  
Aspartame 0.5%

**Example XXI Good Tasting 9-(S)-Erythromyclamine HCl Powder Suitable for  
Dry Powder Inhalation**

9-(S)-erythromyclamine 83.0%

HCl 6.5%

1,2-Distearoyl-sn-glycero-3-phosphocholine 9.3%

CaCl<sub>2</sub> 0.7%

Ethyl vanillin 0.5%

[0073] As those skilled in the art will appreciate, numerous changes and modifications can be made to the many disclosed embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention. It is intended that each of the patents, applications, and printed publications including books mentioned in this patent document be hereby incorporated by reference in their entirety.

What is claimed is:

1. A dry powder formulation comprising:  
a drug substance(s) 1% – 95% by weight; and  
a taste masking agent(s) 0.01% - 95% by weight, wherein the at least one drug substance has an average particle diameter size between about 1 and about 10 microns and the one or more taste masking agents have an average particle diameter size greater than about 10 microns.

2. The dry powder formulation of claim 1, which formulation comprises:  
a drug substance(s) 1% – 95% by weight;  
a taste masking agent(s) 0.01% - 95% by weight;  
a surfactant(s) 0.5% – 95% by weight, wherein the drug substances has an average particle diameter size of between about 1 and about 5 microns and the one or more taste masking agents has an average particle diameter size of between about 20 and about 150 microns and the one or more taste masking agents is selected from a group consisting of sweeteners, fragrances and flavorants, or combinations thereof.

3. The dry powder formulation of claim 1, the formulation comprising  
a drug substance(s) 1% – 95% by weight;  
a taste masking agent(s) 0.01% - 95% by weight;  
a surfactant(s) 0.5% – 95% by weight,  
a particle rigidifying excipient(s) 0.1% - 20% by weight wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents has an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

4. The dry powder formulation of claim 1, the formulation comprising  
a drug substance(s) 30% – 85% by weight;  
a taste masking agent(s) 0.01% - 55% by weight;  
a surfactant(s) 0.5% – 10% by weight,



a particle rigidifying excipient(s) 0.1% - 5 % by weight, wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, or combinations thereof.

5. The dry powder formulation of claim 1, the formulation comprising  
a drug substance(s) 1% – 95% by weight;  
a taste masking agent(s) 0.01% - 5% by weight;  
1,2-distearoyl-sn-glycerol-3-phosphatidylcholine 0.5% – 95% by weight,  
a particle rigidifying excipient(s) 0.1% - 20% by weight, wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

6. The dry powder formulation of claim 1, the formulation comprising  
a drug substance(s) 1% – 95% by weight;  
a taste masking agent(s) 0.01% - 5% by weight;  
1,2-distearoyl-sn-glycerol-3-phosphatidylcholine 0.5% – 95% by weight,  
CaCl<sub>2</sub> 0.1% - 20% by weight, wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

7. A dry powder formulation comprising:  
tobramycin 1% – 95% by weight;  
a taste masking agent(s) 0.01% - 5% by weight;  
1,2-distearoyl-sn-glycerol-3-phosphatidylcholine 0.5% – 95% by weight; and  
CaCl<sub>2</sub> by weight 0.1% - 20%, wherein the tobramycin has an average particle diameter size of between about 1 and about 5 microns and the one or more taste masking agents has an average particle diameter size of between about 20 and about 150 microns and

the one or more taste masking agents is selected from a group consisting of sweeteners, fragrances and flavorants, or combinations thereof.

8. The dry powder formulation of claim 7, the formulation comprising tobramycin 50% – 80% by weight;

sulfate 15% – 25% by weight;

taste masking agent(s) 0.01% - 5% by weight;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine 1-5% by weight;

CaCl<sub>2</sub> 0.1% - 20% by weight, the tobramycin has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

9. A dry powder formulation comprising:

9-(S)-Erythromyclamine 1% – 95% by weight;

a taste masking agent(s) 0.01% - 95% by weight wherein the 9-(S)-erythromyclamine has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.

10. The dry powder formulation of claim 9, the formulation comprising

9-(S)-Erythromyclamine 60% – 95% by weight;

HCl 5% – 10% by weight;

A taste masking agent(s) 0.01% - 25% by weight;

1,2-distearoyl-sn-glycerol-3-phosphatidylcholine 5% – 25% by weight;

CaCl<sub>2</sub> 0.1% - 1.0% by weight, wherein the at least one drug substance has an average particle diameter size between about 1 and about 5 microns and the one or more taste masking agents have an average particle diameter size between about 20 and about 150 microns and the one or more taste masking agents are selected from a group consisting of sweeteners, fragrances, flavorants, and combinations thereof.